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Efficacy of Turmeric (*Curcuma longa*) Extract and Selenium against *Nerium indicum* Induced Toxicity in the Kidney of Wistar Rats

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Abstract: Wistar rats were treated as Group A: Control; Group B: *Nerium indicum* leaves extract (NLE) (25 mg/kg b wt); Group C: *Nerium indicum* leaves extract (25 mg/kg b wt) and Selenium (0.5 mg/kg b wt) (NLE + Se); Group D: *Nerium indicum* leaves extract (25 mg/kg b wt) + *Curcuma longa* rhizomes extract (200 mg/kg b wt) (NLE + CRE); Group E: Selenium (Se) (0.5 mg/kg b wt) and Group F: *Curcuma longa* rhizomes extract (CRE) (200 mg/kg b wt). Serum uric acid, creatinine and urea levels were analyzed on day 15 and 30.

Nerium leaf extract exposure (group B) to rats provoked increased serum uric acid on day 15 and 30. Uric acid decreased in group C and group D on day 15 and 30 as compared to rats of group B. No alteration in uric acid level was seen in Se (group E) and CRE treated rats (group F) at day 15 and 30 as compared to group A i.e. control.

In the present study, creatinine levels increased in rat of Group B (treated with NLE) on 15 day and 30 day as compared to control (group A). Serum creatinine level significantly decreased after treatment with combination of NLE and Se (group C) and NLE and CRE (group D) at 15 day and 30 day as compared to Group B (only NLE treated). In Se (group E) and CRE treated rats (group F) at day 15 and 30 the creatinine levels remained unaffected as compared to group A i.e. control.

Serum urea levels increased significantly in rat of group B (NLE) from 15 day to 30 day as compared to control (group A). Serum urea levels decreased progressively from 15 day to 30 day after treatment with NLE and Se (group C) or NLE and CRE (group D as compared to Group B (NLE exposed). In Se (group E) and CRE treated rats (group F) at day 15 and 30 the urea levels showed no alterations as compared to group A i.e. control. Serum urea levels remained unaltered on day 15 and day 30 in group E and F as compared to control (group A)

Keywords: Botanical pesticides, *Curcuma longa*, Selenium, *Nerium indicum*, Kidney toxicity

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Introduction

To cope with the necessities of the food, the use of pesticides in agricultural fields increasing uncontrollably to control, eradicate or kill the pests. The uses of pesticides all over the world are two million tons per year (Mossa *et al*., 2018). The pesticide affects the living organisms directly or indirectly causing imbalance in environment and nature. A report given by WHO (World Health Organization) described that 80% of total world population depends on botanicals to cure diseases (Al-Attar and Al-Taisan, 2010; Omwenga *et al*., 2015). The use of botanical pesticides instead of synthetics is more convenient, which is cheap, easily available, less accumulate in environment, easily degradable, less effects on non-targets organisms and have very short life period (Fartyal and Kumar, 2014). Despite their less effectiveness to non-target organisms, it caused severe damages in nature if not used brilliantly. *Nerium indicum* plants have great ability to tolerate heavy metals like lead and cadmium contamination in soil (Jamil *et al*., 2023).

Nerium indicum is ornamental plant mostly found near the bank of river, roadsides and gardens (Adome *et al*., 2003). Secondary metabolites or active chemicals are obtained from all part of *Nerium indicum* (Family- Apocynaceae) plant contains neritaloside, odoroside A, odoroside H, adynerin, 12β-D-hydroxypregna 4,6,16-trien-3,2,20-dione, thevetin B, theventin A, neriifolin, monoglycocidic cardenolides, oleandrin, daneric acid, neriuco-umaric acid and vandero-side, odoroside, (Bandara *et al*., 2010; Banerjee *et al*., 2011; Pillay and Sasidharan, 2019; Carfora *et al*., 2021; Rashan *et al*., 2023). Mortality in Sheep (Adam *et al*., 2001) and bees (Harizia, 2015) are noted after exposure with *Nerium* leaves and flowers. High concentration of *Nerium indicum* active chemical is analyzed in blood, heart, liver, kidney, lung and spleen (Jin-Xio *et al*., 2018; Thomas *et al*., 2022; Pugliese *et al*., 2024). In rabbit decrease in body weight and increase in body temperature have been reported by Al-Farwachi *et al*. (2008) due to *Nerium* poisoning. Phyto-chemicals from *Nerium oleander* are toxic and cause constant urination and necrosis of tubules in kidney (Jassim *et al*., 2022). A case report studies showed that women lost her life by drinking tea made with *Nerium* leaves and in other case the women suggested to take *Nerium* leaves for treatment, showed symptoms like vomiting, abnormal heart rate and bradycardia (Khan *et al*., 2010; Dey *et al*., 2022). There is another case of *Nerium* poisoning where man lost his life due to multi organ collapse, cardiac blockage and cardiac arrest (Wasfi *et al*., 2008; Anandhi *et al*., 2019; Patil and Agrahari, 2020; Carfora *et al*., 2021; Bandyopadhyay *et al*., 2023; Beniwal *et al*., 2023). *Nerium oleander* is used as antibacterial, anti-inflammatory (Safiq *et al*., 2021), cardiovascular protective (Khan *et al*., 2010; Adome *et al*., 2003), antioxidant (Mohale *et al*., 2016), Anti- anxiety (Shashikala *et al*., 2018), Immune modulator (Al-Farwachi, 2007; Dey and Chaudhuri, 2016), abortifacient and treatment of cardiac failure in human being (Abdou *et al*., 2019).

Selenium is a dietary supplement and small amount is essential for normal growth and development in animal and human body (Ralston and Laura, 2010; Fatma *et al*., 2023; Rao *et al*., 2024). Selenium have antioxidant, anti-cancerous, anti-tumor, hepato-protective (Newairy *et al*., 2007) and nephro-protective (Al- Sharanky *et al*., 2007; Aksoy *et al*., 2015) capability to recover from damages caused by toxic substances. *Curcuma longa* (family Zingiberaceae) plants is a herbaceous, perennial, native to southeast India and mostly farmed in tropical region of south Asia. Turmeric contains yellow pigment which is used in spices, food color, and as dye agent in numerous textile companies. Yellow pigment present in turmeric is curcumin which have very little absorbance properties in human (Labban, 2014; Leong, 2018). 100 active secondary metabolites of *Curcuma longa* are recognized worldwide (Hosseini and Hosseinzadeh, 2018; Fluroia *et al*., 2022). Curcumin (diferuloyl-methane) contains 1, 7-bis (4-hydroxy-3methoxyphenyl)- 1, 6- heptadien- 3,5-dione, an active chemical substance which is antioxidant,

ant-inflammatory, anti-proliferative by inhibition of ROS formation due to stress (Ravindran *et al*., 2010). *Curcuma longa* possesses properties of anti-cancerous, anti-cardiac (Mohanty *et al*., 2004), anti-diabetic, anti-stress (Madhushudhan *et al*., 2010), wound healing (Thakre *et al*., 2011; Purohit *et al*., 2013; Pawar *et al*., 2015), hypertension reducer (Xia *et al*., 2016), Anti-ulcergenic (Airaodion *et al*., 2019), and anti-Alzheimer (Kumar *et al*., 2009). Kidney and liver are vital organs which play important function to discard the pesticides toxicity out from animal and human biological system (Sharma and Sangha, 2014).

The present study investigated the alternation in kidney function parameters such as serum uric acid, creatinine and urea of *Nerium indicum* leaves extract exposed Wistar rats. The study also evaluated the possible ameliorative effects of selenium and *Curcuma longa* rhizomes extract on kidney biomarkers of *Nerium indicum* leaves extract exposed rats.

Materials and Methods

Total 120 Wistar rats (weight 40-50 g) were obtained from Asia Scientific Emporium, Varanasi, India. Animals are acclimatized for 14 days in lab. Throughout the experiment proper diet and water was provided *ad libitum*. *Nerium indicum* (25 mg/kg b wt) leaves extract, Selenium (Se) (0.5 mg/kg b wt) and *Curcuma longa* (200 mg/kg b wt) rhizome extract were given orally to the rats. These doses were selected on the basis of doses given by previous investigators (Altaee, 2011; Joshi *et al*., 2013, 2017). Fresh leaves of *Nerium indicum* were collected from roadsides and fresh *Curcuma longa* rhizomes were obtained from the local market of Gorakhpur, Uttar Pradesh, India. Fresh leaves and rhizomes were washed with tap water to remove dust particles and dried at room temperature under shade. Dried leaves and rhizomes were crushed in grinder to make fine particles. These crushed leaves and rhizomes were put separately in 90% ethanol (1:20 ratio) and filtered with Whatman no. 1 filter paper. Supernatant was kept in oven at 35°C to dry and these dried residues were kept for future study. To protect heat labile compounds in the plants extracts, Soxhlet was not used for extraction. Prepared doses were given orally with the help of gavage at 8:00 am daily.

Rats were randomly divided into 6 numerically equal groups- A, B, C, D, E and F and treated daily for 30 days as follow:

Group A: Control

Group B (*NLE*): *Nerium indicum* leaves extract (25 mg/kg b wt)

Group C (*NLE + Se*): *Nerium indicum* leaves extract (25 mg/kg b wt) and Selenium (0.5 mg/kg b wt)

Group D (*NLE + CRE*): *Nerium indicum* leaves extract (25 mg/kg b wt) + *Curcuma longa* rhizomes extract (200 mg/kg b wt)

Group E (*Se*): Selenium (0.5 mg/kg b wt)

Group F (*CRE*): *Curcuma longa* rhizomes extract (200 mg/kg b wt)

Rats were sacrificed under light anesthesia after the last day of treatment (15th day and 30th day). Before sacrifice rats were fasted overnight. Blood was collected by cardiac puncture and centrifuged at 3000 rpm. Sera were collected and kept at -20°C for further use. Serum uric acid, creatinine and urea were measured with the help of commercial kit (Beacon Diagnostics Private Ltd. India). Each sample was analyzed in duplicate.

Statistical Analysis: Each data represents mean ± Standard Error (S.E) of six specimens. For multiple group comparisons, one way Analysis of Variance (ANOVA) was used. Differences between groups were tested by Student's t test and Bonferroni post hoc test. The $p<0.05$ was set for statistical significance.

Results

Nerium leaf extract exposure (group B) to rats provoked increased serum uric acid on day 15 and 30 (Fig. 1). Uric acid decreased in group C and

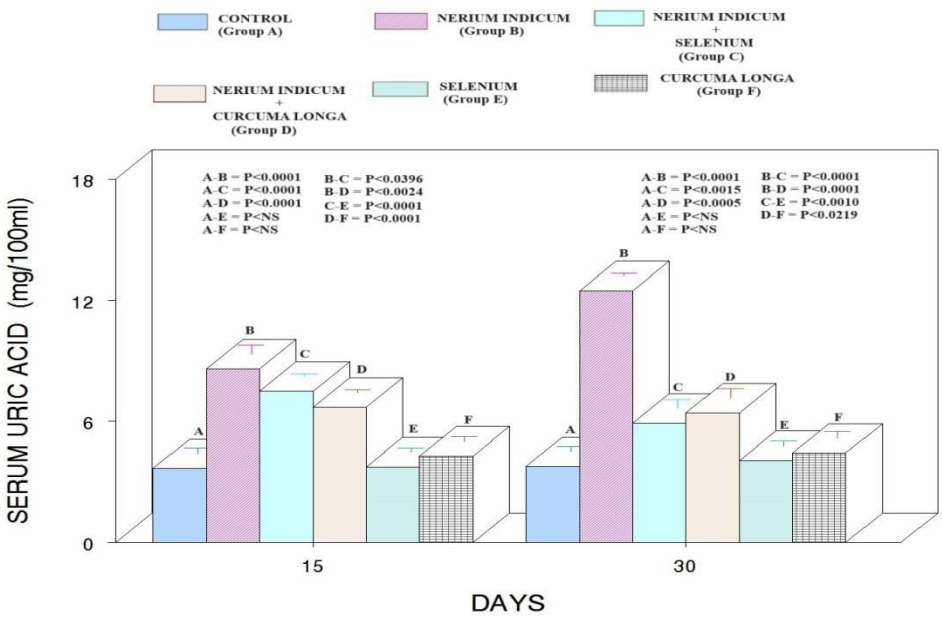

Fig. 1: Serum uric acid levels (mg/100 ml) of Wistar rats: Control (group A), NLE (group B), NLE + Se (group C), NLE + CRE (group D), Se (group E) and CRE (group F). Each value indicates Mean + S.E. for six specimens.

group D on day 15 and 30 as compared to rats of group B. No alteration in uric acid level was seen in Se (group E) and CRE treated rats (group F) at day 15 and 30 as compared to group A i.e. control. Analysis of variance (ANOVA) indicated that treatment is significant (day 15-- F= 65.314; P< 0.0001; day30-- F = 96.093; P< 0.0001).

In the present study, creatinine levels increased in rat of Group B (treated with NLE) on 15 day and 30 day (Fig. 2) as compared to control (group A). Serum creatinine level significantly decreased after treatment with combination of NLE and Se (group C) and NLE and CRE (group D) at 15 day and 30 day as compared to Group B (only NLE treated). In Se (group E) and CRE treated rats (group F) at day 15 and 30 the creatinine levels remained unaffected as compared to group A i.e. control. ANOVA indicated that treatment is significant (day 15; F = 7.358; P< 0.0001; day 30; F = 58.005; P< 0.0001).

Serum urea levels increased significantly in rat of group B (NLE) from 15 day to 30 day (Fig. 3) as compared to control (group A). Serum urea levels decreased progressively from 15 day to 30 day after treatment with NLE and Se (group C) or NLE and CRE (group D) as compared to Group B (NLE exposed). In Se (group E) and CRE treated rats (group F) at day 15 and 30 the urea levels showed no alterations as compared to group A i.e. control. Serum urea levels remained unaltered on day 15 and day 30 in group E and F as compared to control (group A). ANOVA indicated that treatment is significant (day 15; F = 26.015; P< 0.0001; day 30; F = 40.777; P<0.0001).

Discussion

In the present study, *Nerium* leaf extract exposure to rats provoked alternations in the kidney bio-markers which is evident by increased urea, creatinine and uric acid levels. Similar results have also reported by earlier investigators after exposure of toxicants from rats-- Acrylamide (Uthra *et al*., 2022), Deltamethrin (Mostafa *et al*., 2022), Cadmium (Ilesanmi and Adeogun, 2022), Paraoxon (Sobolev *et al*., 2021), Methotrexate (Alum *et al*., 2023), Dimethoate (Fatma *et al*., 2023), Oxazaphosphorine (Lukasz *et al*., 2017),

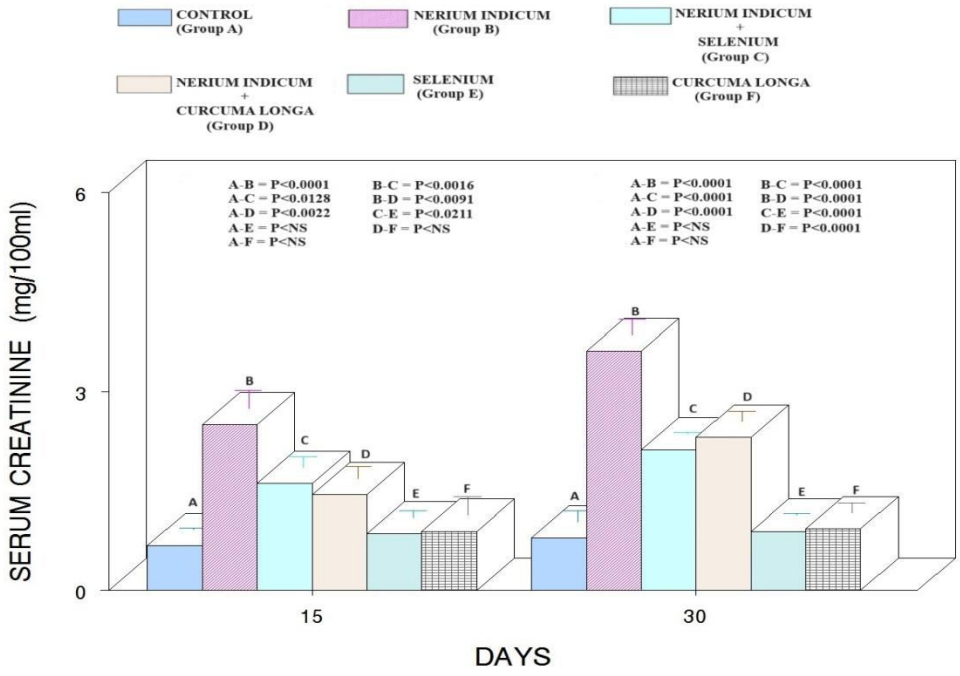

Fig. 2: Serum creatinine levels (mg/100 ml) of Wistar rats: Control (group A), NLE (group B), NLE + Se (group C), NLE + CRE (group D), Se (group E) and CRE (group F). Each value indicates Mean + S.E. for six specimens.

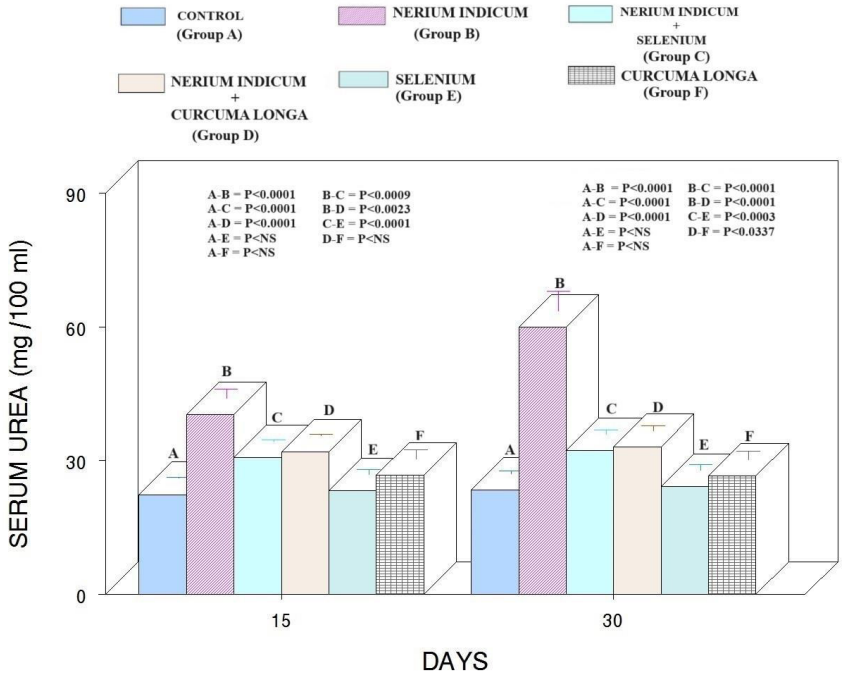

Fig. 3: Serum urea levels (mg/100ml) of Wistar rat: Control (group A), NLE (group B), NLE + Se (group C), NLE + CRE (group D), Se (group E) and CRE (group F). Each value indicates Mean + S.E. for six specimens.

Tartrazine (Desoky *et al*., 2022), Chlorpyrifos (Aung *et al*., 2020) Gentamicin (Akhitha *et al*., 2019) and mice-- Chromium (Abbas *et al*., 2016). Alterations in kidney biomarkers have also been observed by other workers after exposure to various toxicants in – (i) fishes-- Indoxacarb (Ali *et al*., 2018), Bisphenol A (Srivastava and Reddy, 2020), Diazinon (Banaee *et al*., 2023), Imidacloprid (Qadir *et al*., 2014) and Deltamethrin (Hamed, 2016); and (ii) Amphibian-- Cadmium (Medina *et al*., 2016) and Oxyfluorfen (Ghada *et al*., 2019). In the present study, there is a significant decrease in the levels of serum urea, creatinine, serum uric acid in NLE exposed rat after treatment with Se (group C) and CRE (group D) which clearly indicated preventive effect of Se and CRE against NLE induced nephrotoxicity.

An increased level of serum creatinine in rats has been noticed in the foregoing study after NLE exposure which is in conformity with report of Eivani *et al*. (2023) who have also noticed increase in serum creatinine levels of lead treated rat. In group C (NLE+Se) and group D (NLE+ CRE), the creatinine levels decreased on 15 day and 30 day in comparison to Group B (NLE treated rats). This indicates that Se and CRE are effective in protecting kidney and improved the serum creatinine levels which was increased after treatment with *Nerium* leaf extract. There was no change observed in creatinine levels after treatment with selenium or *Curcuma longa* rhizomes extract to rat. Earlier to this study there exists no report regarding the effects of Se and CRE on creatinine levels of *Nerium* leaf extract exposed rats. Joshi *et al*., 2013 reported normal serum urea, creatinine and uric acid in rat after treatment with *Curcuma longa* against mercuric chloride toxicity.

In *Nerium* leaf extract exposed rats, increased serum urea levels were recorded at 15 day and 30 day. This is supported by the observations of earlier investigators who have also noticed increased serum urea levels in toxicants exposed rats—Bisphenol A (Kobroob *et al*., 2018); Cypermethrin and chlorpyrifos (Ajobola *et al*., 2019); cypermethrin (Sankar *et al*., 2012, Kheirallah *et al*., 2021); Arsenic (Yousuf et al., 2023); Tartrazine (Rahayu *et al*., 2022) and Acetaminophen (Roy *et al*., 2015). Treatment with *Nerium* leaf extract in combination with Se or CRE decreased serum urea levels significantly as compared to Group B (only *Nerium* leaf extract treated rat). Serum urea levels in rat remained unaffected after exposure to with Se or CRE. El-Boshy *et al.* (2015) reported normal serum urea, creatinine and uric acid when rat was treated with selenium against toxicity caused by cadmium. In past no report has been made regarding the effects of Se or CRE on *Nerium* leaf extract induced alterations in serum urea of rat.

In the present study exposure of *Nerium* leaf extract to rats induced a significant increase in serum uric acid levels in comparison to control (group A) from 15 day to 30 day. The observations of this study is in conformity with findings of Ashour *et al.* (2007) who have reported increased serum uric acid levels in lead exposed rat. The combined dose of *Nerium* leaf extract with selenium or *Curcuma longa* rhizomes extract was given to the rat which significantly reduced levels of serum uric acid. This is evident that Se and *Curcuma longa* rhizomes extract play protective role against *Nerium* leaf extract induced toxicity in recovering uric acid levels to nearly control values.

Conclusion

It is concluded that *Nerium* leaf extract provoked alterations in serum uric acid, creatinine and urea levels of rats. There is a significant decrease in the levels of serum urea, creatinine, serum uric acid in NLE exposed rat after treatment with Se (group C) and CRE (group D) which clearly indicated preventive effect of Se and CRE against NLE induced nephrotoxicity.

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